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SYNTHESIS AND CHARACTERISATION OF DIHYDROPYRIMIDONE DERIVATIVES EMPLOYING THE BIGINELLI REACTION CATALYSED BY A COPPER BASED NOVEL REAGENT

Chemistry

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ABSTRACT

A new protocol for the synthesis of a series of dihydropyrimidone derivatives is reported in this paper. The three component condensation of aromatic aldehyde, urea and ethyl acetoacetate is carried out in presence of a copper based novel catalyst prepared from O-phenylene diamine and copper acetate. This catalyst is effective in making of the dihydropyrimidone derivatives in excellent yield. The products are purified by the recrystallization technique and are characterised by the IR and PMR spectroscopy. Dihydropyrimidones are the vital skeleton for the biologically active compounds hence its synthesis is very important. The different variants with modified reactivity are also reported in the literature hence this synthetic method can provide an insight for the preparation of them as well. The removal of catalyst is easy and the overall synthetic method is convenient and free of any side products.

KEYWORDS

Biginelli, Novel copper catalyst, dihydropyrimidone, O-phenylene diamine

INTRODUCTION:

The Italian chemist Pietro Biginelli reported the synthesis of 3,4-dihydropyrimidin- 2(1*H*)-ones for the first time, by a simple one-pot condensation reaction of an aromatic aldehyde, urea, and ethyl acetoacetate in ethanol solution[1]. The Biginelli reaction has been intensively studied in the last two decades, especially due to the applications of dihydropyrimidone derivatives as calcium channel blockers of the nifedipine-type[2] and then as antitumor[3], antibacterial, antiviral[4], anti-inflammatory[5], analgesic[6], anti-Alzheimer[7], or antioxidant[8] compounds. Dihydropyrimidone derivatives are the backbones of the biologically active natural products with a wide range of therapeutic use. Their major applications include treatment of hypertension, in the treatment of stable angina, Raynaud's syndrome and cerebral vasospasm. Since these compounds are important scaffolds, their syntheses are of great importance. Many syntheses of dihydropyrimidone derivatives have been reported in a scientific literature over a period of 100 years. The 3,4-Dihydropyrimidin-2(1*H*)-ones were synthesised in high yields by one-pot three component Biginelli condensation in ionic liquids such as 1-*n*-butyl-3-methylimidazoliu tetrafluoroborate ($BMImBF_4$) or hexafluorophosphorate ($BMImPF_6$) as catalysts under solvent-free and neutral conditions [9].

A Novel efficient and simple synthetic protocol for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones by using L-proline as the catalyst under solvent free condition[10]. Dicalcium phosphatedihydrate (DCPD) was used as a green and reusable catalyst in order to synthesized two important categories of heterocycles, 3,4-dihydropyrimidin-2-ones and 3,4- dihydropyrimidin-2-thiones [11]. [Hmim] [Tfa] [12] was used as catalyst for the Biginelli reaction under microwave heating. The proposed protocol was found active in the synthesis of different biologically active compounds. A simple and practical route for the Biginelli cyclocondensation reaction using anhydrous $ZnCl_2$ as a catalyst in n-heptane-toluene medium by reaction of substituted benzaldehydes [13] has been reported. A sustainable, green one pot process for the synthesis dihydropyrimidones by a three component reaction of β-ketoester derivatives, aldehyde and urea or thiourea over the alkali treated H -ZSM-5 zeolite under ball-milling was developed [14].

Use of (MImH)(OAc) as a catalyst has been reported in the literature for the cyclocondensation reaction in best yield [15]. The synthesis of 3,4-dihydropyrimidones or thione has been effected by the use of potassium tert-butoxide in excellent yields [16]. ^{13}C NMR spectra and elemental analyses. Among N-methylimidazolium acetate [MImH] [OAc], N-methylimidazoliTrifluoroacetate [MImH] [CF_3CO_2], 4-N, N-dimethylaminopyridinium acetate [DMAPH] [OAc] and 4 N,N-dimethylaminopyridinium trifluoroacetate [DMAPH] [CF_3CO_2], [MImH] [OAc] provide the best result of cyclocondensation reaction[15]. The best results for Biginelli reaction[15].

The synthesis of various substituted Biginelli 3,4-dihydropyrimidinone thione and Hantzsch 1,4- dihydropyridine derivatives has been achieved potassium ter-butoxide (t-BuOK) as a catalyse under solvent-free conditions, in good to excellent yields[16] NBS [17] has been used as a mild, efficient and almost neutral catalyst for the preparation of dihydropyrimidones (DHPMs) and the corresponding thio-derivatives under microwave irradiation. A wide variety of DHPMs were synthesized in good to high yields. A practical and general microwave-mediated Biginelli cyclocondensation of guanidine with aldehydes and β-dicarbonyl compounds provides functionalized 2-amino-3,4-dihydropyrimidines in good yields, with short reaction times and a simple workup. The scope is considerably wider than that of similar reactions carried out under conventional heating. $CaCl_2$[18] is an efficient, inexpensive and readily available catalyst for the three component, one-pot condensation reaction of an aldehyde, β-ketoester and urea in refluxing ethanol to afford the corresponding dihydropyrimidones in high yield.

MATERIALS AND METHODS:

Experimental Procedure:

Preparation of a Reagent: In a 50 mL round bottom flask 1 g of o-phenylene diamine and 1.68 g of copper acetate was charged and the mixture was stirred for 20 minutes. The resultant mixture was cooled, filtered and dried at 100 °C for 1 hr. The product is brown solid m.p. 194 °C. The product was characterised by IR, ^1H NMR, EDAX techniques .

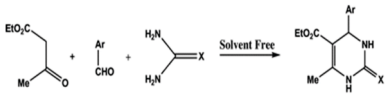
^1H NMR (DMSO-d6): 6.36-6.48, 6.97, 7.50, 7.97, 12.96 IR cm^{-1} : 3800, 3600, 2280, 1600, 1500, 500

EDAX Analysis : C = 70.33 %, N =18.80 %, O = 9.49 %, Cu = 1.38 %

Synthesis of 3,4 –dihydro pyrimidone derivatives: A General Procedure

Benzaldehyde 1 g (9.4 mmole) , Urea 0.56 g (9.4 mmol) and Ethyl acetoacetate 1.2 g (9.4 mmol) were taken in a 50 mL round bottom flask . Catalyst 100 mg and 20 mL ethyl acetate was added to it and the reaction was refluxed for 4 hrs. The reaction mixture was filtered to remove the catalyst and solvent evaporation furnished the crude product. Recrystallization through ethanol furnished the pure product. The products were characterised by IR and ^{1} HNMR spectroscopic techniques.

Scheme 1



X= O

1. Ar = Ph
2. Ar = 4-Cl-Ph
3. Ar = 2-NO_2 – Ph
4. Ar = 4-OH, 3-Ome
5. Ar = 4- Methoxy Phenyl

Spectral Data:

1. Ethyl -6-methyl-4-(4-Phenyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate

IR cm^{-1} 3318, 1720, 1649, 1600, 1512, 1212 ^{1}H NMR 1.14 t, 3H, 2.26, s, 3H, 3.91 ,q, 2H , 5.12 , d, 1H, 5.90 , s, 1H , 7.3 (m, 5H) 9.09, s, 1H

2. Ethyl-6-methyl-4-(4-chlorophenyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate

IR cm^{-1} 3242, 3131, 2929, 1724,1703, 1649, 1487,1466 ^{1}H NMR 1.14 t, 3H, 2.26, s, 3H, 4.02 ,q, 2H , 5.35 , d, 1H, 6.80, s, 1H, 7.2-7.8 m, 4 H , 9.09, s, 1H

3. Ethyl-6-methyl-4-(2-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidinecarboxylate

IR cm^{-1} 3443, 3149, 2998, 1676, 1592, 1517, 1370,1234 ^{1}H NMR (400 MHz, $CDCl_3$) 1.17 t, 3H, 2.32, s, 3H, 4.08 ,q, 2H , 5.13 , d, 1H, 6.43-6.95 m, 4H , 9.57, s, 1H , 10.2 s, 1H

4. Ethyl-6-methyl-4-(4-hydroxy,3-methoxyphenyl)-2-oxo-1,2,3,4-tetrahydro-5- pyrimidinecarboxylate

IR cm^{-1} 3360, 3276, 1640, 1471,, 1417, 1083 ^{1}H NMR 1.4 t, 3H, 2.32, s, 3H, 3.7 s, 3H, 4.7 ,q, 2H , 5.13 , d, 1H, 7.65-8.2 m, 3H , 9.12, s, 1H, 9.8 s, 1H

5. Ethyl-6-methyl-4-(methoxyphenyl)-2-oxo-1,2,3,4-tetrahydro-pyrimidinecarboxylate

IR cm^{-1} 3242, 2955, 1708, 1649, 1612, 1512, 1460 ^{1}H NMR 1.15 t, 3H, 2.25, s, 3H, 3.73 s, 3 H, 4.02 ,q, 2H , 5.13 , d, 1H, 6.83=7.18 m , 4H , 7.57 s,1H, 9.06, s, 1H

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